

We believe Doctor Read's finding, that some of his patients originally reported as only "improved" but not completely cured, and found to be completely cured after an average elapsed time of seven years, is rather a common observation in irradiated cases of thyrotoxicosis. We have observed a number of similar cases in our clinic.

Apparently none of the four patients in Doctor Read's table classed as "chronic" received adequate roentgen dosage. As all of these patients showed improvement, additional dosage would probably have produced permanent relief. One patient who showed a reduction in metabolism from plus 54 to plus 10 had received only 1140 r and was only under observation one year. Another patient was reduced from plus 55 to plus 27, although she only received a total of 800 r, which is usually an entirely inadequate total dosage.

Doctor Read's paper again demonstrates clearly and very scientifically that thyrotoxic patients who receive adequate radiation dosage do get well and remain well.

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JOHN HUNT SHEPARD, M. D. (Medico-Dental Building, San Jose).—It is from such reports as Doctor Read has given us, based on years of careful observation, that medical knowledge is increased.

Patients afflicted with Graves' disease have returned to health after receiving most varied kinds of treatment or no treatment at all, and therefore it becomes most difficult to evaluate properly any form of treatment unless the response to it is prompt and definite.

I cannot become enthusiastic over irradiation in thyrotoxicosis when one patient returns to health after receiving a dosage of but 200 r to each lobe of the thyroid gland while another will receive 4000 r, or more, over a period of many weeks or months with little or no abatement of symptoms. Although irradiation in Graves' disease has been used for many years, and we have heard a great deal about "adequate dosage," we have been given no definite information as to what is adequate.

In CALIFORNIA AND WESTERN MEDICINE, July 1925, I wrote "... it is irrational to destroy a portion of any factor to curtail its output ..." but when we do a subtotal thyroidectomy, leaving glandular tissue equivalent in volume to one-fourth the amount of a normal thyroid gland, at least 75 per cent of our thyrotoxic patients return to normal health within six months, and of those upon whom we operate within two months of the onset of their symptoms, the percentage of cures is higher and the time required for complete relief of symptom is shorter.

Those favoring nonsurgical treatment of thyrotoxicosis seem to keep before their minds the so-called surgical fatalities and postoperative myxedema and tetany. A careful study of the records of these surgical failures show that the vast majority are analogous to the records of patients with appendicitis when they were given the benefit of four or five days' treatment before operation, and though we all have seen patients recover from an attack of appendicitis under nonsurgical treatment and occasionally have seen a patient die following an early simple appendectomy, most of us agree that early surgical intervention is the proper procedure.

As I wrote in 1925, "I look forward to the time when thyroidectomy will not be the treatment for this disease, ..." but in the light of our present knowledge greater success is obtained by a properly performed thyroidectomy than by any other treatment.

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DOCTOR READ (Closing).—It seems quite fitting that an internist, a roentgenologist, and a surgeon should discuss this paper for, as Doctor Costolow reminds

us, this is a disease of questionable or unknown etiology for which there is no specific treatment, and its proper handling often requires the coöperation of several specialists. The plan of study outlined by Doctor Kerr should broaden the viewpoint of every physician who participates in the conference long enough to obtain late follow-up data. Doctor Kerr intimates that they are demonstrating that the same is true of thyrotoxicosis that is true of almost every other disease, namely, there are some patients who recover with any or no treatment, and at the other extreme there are a few which resist every form of therapy. A very similar viewpoint was expressed upon this subject by me in 1926 (February) in the *American Journal of the Medical Sciences*.

I am grateful to Doctor Costolow for emphasizing again that beneficial results may not follow until two or three months after institution of treatment, and that it is necessary in some patients to repeat the treatments in six to twelve months. He has pointed out the tendency toward using heavier dosage, which is the crux of the matter in successful irradiation for thyrotoxicosis. What constitutes adequate dosage in any given case is difficult to determine, but we have progressed to the point where we are sure a patient has not been adequately treated until he has been given much heavier dosage than it has been customary in the past. We cannot, therefore, enlighten Doctor Shepard as to what constitutes "adequate dosage" and we are as much in the dark as to what constitutes "a properly performed thyroidectomy." Many such operations which seemed properly performed have not been attended by the anticipated results.

### CINCHOPHEN ADMINISTRATION— JAUNDICE AS AN UNTOWARD EFFECT\*

#### REPORT OF CASES

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AND

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FOLLOWING the introduction of cinchophen into materia medica by Nicolaier and Dohrn<sup>1</sup> in 1908, its use became widespread owing to its remarkable pain-relieving properties in arthritic and neuritic conditions. For fifteen years its reputation was unassailed, except by an occasional report of a minor toxic manifestation. However, Worster-Drought<sup>2</sup> in 1923 reported a case of severe jaundice following the ingestion of atophan. Cabot<sup>3</sup> in 1925 described a case of fatal poisoning by a preparation (weldona) containing cinchophen. The necropsy showed an extensive parenchymatous degeneration of the liver. Since the appearance of Cabot's report a number (thirty-two) of fatal cases of cinchophen poisoning have appeared in the literature. Postmortem examination of these cases has invariably demonstrated severe liver damage characterized by

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widespread necrosis of the hepatic cells, round cell infiltration and marked diminution in the size of the organ ("yellow atrophy").

#### THE PATHOGENESIS OF JAUNDICE IN CINCHOPHEN POISONING

The pharmacologic action of cinchophen upon the liver has been shown by Brugsch and Horsters<sup>4</sup> to be due primarily to direct stimulation of the polygonal hepatic cells. The quantity of bile excreted was shown to be considerably increased. It is a well-established toxicologic principle that poisons, which in minimal doses stimulate, paralyze in maximal doses. A preliminary report of work done by Churchill and Van Wagoner<sup>5</sup> seems to confirm this principle in cinchophen intoxication. They found areas of acute necrosis in the livers of dogs killed by large doses of cinchophen.

It is generally accepted at present that the bile pigments are formed by the reticulo-endothelial system<sup>6</sup> and are excreted into the biliary passages by the activity of the polygonal hepatic cells. In hepatic necrosis the jaundice results from an inability of the polygonal cells to function in this capacity of bile excretion.<sup>7</sup> In cinchophen poisoning the degree of hepatic necrosis varies; consequently there may result varying degrees of jaundice, depending upon the extent of the lesion in the liver. Fortunately not every case develops to the degree of icterus gravis.

#### SYMPTOMATOLOGY AND DIAGNOSIS

A diverse symptomatology due to cinchophen intoxication has been described. We<sup>8</sup> have previously classified these manifestations as follows:

"1. Cutaneous manifestations, such as pruritus, angioneurotic edema, urticaria, macular and papular rashes, first reported by Phillips<sup>9</sup> in 1913;

"2. Anaphylactoid reactions characterized by neuro-circulatory disturbances associated with rapid pulse and lowered blood pressure following the ingestion of single doses of cinchophen, as mentioned by Scully<sup>10</sup> in 1924;

"3. Gastro-intestinal disturbances including simple aphthous ulcers in the mouth, pyrosis, nausea, vomiting, and diarrhea, reported by Schroeder<sup>11</sup> in 1922; and

"4. Liver involvement as indicated by the appearance of jaundice, first noted by Worster-Drought<sup>2</sup> in 1923."

The clinical diagnosis of this entity, following the appearance of jaundice, is not difficult. A history of the taking of cinchophen followed by the disappearance of pain associated with the onset of jaundice is usually obtained. The physical examination reveals jaundice, the degree of which varies with the severity of the liver damage. In the early stage the liver may be slightly enlarged and tender, but later shows a progressive diminution in size. This may be objectively demonstrated by a flat radiographic plate of the abdomen, following oxyperitoneum. In severe cases the patient is frequently in coma. Laboratory examinations frequently show albumin, casts, and bile in the urine. Tyrosin and leucin crystals may be present in severe cases. The icteric index of the blood serum is increased to as much as 200 units (normal 4-7). Many cases show a moder-

ate secondary anemia. Space does not permit a discussion of the differential diagnosis of this condition from jaundice due to other causes.

#### REPORT OF CASES

CASE 1.†—Mrs. K. H., white, age fifty, was seen by Dr. Caroline Leete on June 3, 1931. In January, 1931, the patient complained of arthritis of the right knee. After a variety of ineffectual treatments, she began in May to take Renton's Hydrocin Tablets.<sup>12</sup> She stated she took eight tablets daily for six days and then five tablets daily, until she had consumed a total of sixty-six tablets. The total amount of cinchophen is, hence, about 330 grains.<sup>12</sup> After taking forty tablets she began to have anorexia, epigastric distress, and nausea. She noticed jaundice after taking sixty-six tablets and discontinued the use of the drug. Physical examination on June 3, 1931, showed severe icterus. The liver was not reduced in size. The examination was otherwise negative. The blood chemistry was normal except for an icteric index of 150. Urine examination showed albumin plus with many hyalin and granular casts, and bile two plus. She was placed on a high carbohydrate diet and put to bed for three weeks. One month later her recovery was practically complete.

CASE 2.‡—Mrs. V. A. M., white, age forty-four, was seen by Dr. J. M. Lacey on June 23, 1931. The patient had been taking cinchophen for three weeks, and had developed severe urticaria on June 20, 1931. At the time of the examination she was jaundiced and had a slight fever. She was sent to the hospital and intravenous (10 per cent glucose in saline) injections were given. Alkalies were administered by mouth. Severe vomiting developed but disappeared in two days. The icterus gradually diminished and complete recovery had taken place in one month.

CASE 3.‡—Mrs. A. S. L., white, age forty-eight, was seen by Doctor Lacey in May, 1930. She had taken a large amount of atophan because of a maxillary sinusitis. The onset of the attack was characterized by swelling of the hands and feet, followed by generalized urticaria. There had been severe nausea and vomiting associated with the attacks. After the subsidence of the urticaria, which persisted for five days, moderately severe jaundice developed. A severe secondary anemia was associated with the jaundice. She recovered gradually and at present is apparently well.

CASE 4.§—Mrs. X., white, age fifty-five, was seen by Dr. J. J. Hilton on December 12, 1930. In September 1930 the patient had taken three Renton's Hydrocin Tablets daily, until a total of fifty tablets had been used for an asserted increase in the uric acid content of her blood as manifested by a small eczematoid patch in the right popliteal space. Three weeks following the completion of the treatment, she noticed burning in throat, anorexia, and general irritability. One week later marked malaise and vomiting appeared. On December 1, 1931, she began to notice jaundice, which deepened progressively. There was an associated severe pain localized to the lumbar region, with radiation along the sciatic nerve. Her past medical history was irrelevant. For the past five years she had limited the carbohydrate intake in her diet in order to control her weight. The physical examination revealed a markedly jaundiced, somewhat stuporous woman with a slightly enlarged liver. The remaining physical findings were normal. The Van den Bergh was positive direct with an indirect read-

† We are indebted to Doctor Leete for permission to publish this case report.

‡ We are indebted to Doctor Lacey for permission to publish these case reports.

§ We are indebted to Doctor Hilton for permission to publish this case report.

ing of 27.75 units. The icterus index was 112. She was treated by supportive measures, including the frequent intravenous administration of glucose solution. The degree of jaundice increased, and on December 17 she lapsed into coma. Death occurred on the following day. A postmortem examination was refused.

#### TREATMENT

At present there is no specific treatment for cinchophen poisoning. It is well established, however, that a liver which is depleted of its glycogen is especially susceptible to the action of poisons. Consequently, the empiric use of intravenous glucose and a high carbohydrate diet appears justified. The administration of alkalis by mouth to combat the acidosis has also been advocated. Bismuth or opiates may be used to control the nausea and vomiting. Further treatment should consist of symptomatic and supportive measures.

#### SUMMARY

1. Thirty-two fatalities due to cinchophen have appeared in the literature.
2. The essential pathology of this condition is a parenchymatous degeneration of the liver.
3. Cinchophen exerts a direct stimulating action on the hepatic polygonal cells.
4. The clinical syndrome of cinchophen poisoning is described.
5. Four cases are reported of cinchophen poisoning showing icterus, one of which was fatal.  
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#### REFERENCES

1. Nicolaier, A., and Dohrn, H.: Über die Wirkung von Chinolincarbonsäuren und ihrer Derivate auf die Ausscheidung der Harnsäure, *Deutsch. Arch. f. klin. Med.*, 93:331, 1908.
2. Worster-Drought, C.: Atophan Poisoning, *Brit. J. Med.*, 1:148 (Jan. 27), 1923.
3. Cabot, R. C.: *Boston M. and S. J.*, 192:1122 (June 4), 1925.
4. Brugsch, T., and Horsters, H.: Cholereise und Choleretica, ein Beitrag zur Physiologie der Galle, *Ztschr. f. d. ges. exper. Med.*, 43:714, 1924.
5. Churchill, T. P., and Van Wagoner, F. U.: Cinchophen Poisoning, *Proc. Soc. Exper. Biol. and Med.*, 28:581 (March), 1931.
6. Aschoff, L.: *Lectures on Pathology*. P. 233. Paul B. Hoeber, Inc., New York. 1924.
7. Rolleston, Sir Humphrey: *Oxford Medicine*, 3:306, 307. Oxford University Press, New York. 1920.
8. Parsons, L., and Harding, W. G.: Cinchophen (Atophan) Poisoning—Report of Four Cases, *Am. J. M. Sc.*, 181:115 (Jan.), 1931.
9. Phillips, J.: Skin Rashes Following the Administration of Atophan, *J. A. M. A.*, 61:1040 (Sept. 27), 1913.
10. Scully, F. J.: Idiosyncrasy to Cinchophen, *J. A. M. A.*, 82:623 (Feb. 23), 1924.
11. Schroeder, K.: Cases of Atophan Poisoning, *Ugesk. f. laeger*, 84:1141, 1922.
12. Renton's Hydrocin Tablets: Bureau of Investigation, *J. A. M. A.*, 96:209 (Jan. 17), 1931.

#### DISCUSSION

JOHN V. BARROW, M. D. (1930 Wilshire Boulevard, Los Angeles).—The foregoing paper is timely in that so much is being written now and so much is being taken for granted regarding the poisoning induced by cinchoninic acid and its derivatives.

Jaundice is given as the major index of saturation, or idiosyncrasy, of this drug. Any symptom or sign guarding against an overdose or allergic idiosyncrasy is of great value to the clinician. Doctor Parsons and Doctor Harding have called attention to this phase admirably. To my mind, they have overemphasized the danger of poisoning in such a way that it becomes a matter of question whether legal complications are not apt to follow any clinical peculiarity attendant on its use. The ambulance chaser may find it more profitable to leave the automobile accident and read our medical journals in order to get his lead for future prosecutions. Much of the work quoted is mere statement and has not been proven by physiology, pharmacology, and histology. The statement is made that the excretion of the bile pigments is interfered with, particularly. In such an event the icterus index, which deals with these pigments, should be far more important as a clinical guide than gross jaundice. The symptomatology ascribed to this drug has also been ascribed in the days of Adami, Opie, and Osler to toxemia from general infections, malaria, syphilis, bacterial intestinal products, and wrongly split food products. The fact that many of these cases are being treated for a chronic infectious metabolic disorder shows that they are susceptible to allergic reactions in which the liver is undoubtedly involved. No effort has been made to prove the liver function normal at the time the treatment was begun.

In the early part of this century Sir William Osler called attention to the fact that the French were reporting thirteen varieties of cirrhosis of the liver from malarial infection alone. They might as easily have claimed that this liver disturbance was induced by the administration of quinin. Any drug may exhibit idiosyncrasies in some patients, and may induce pathological changes much more easily in an organ already diseased. One of the drugs mentioned in Doctor Parsons's paper is so proprietary that its composition may well be considered unknown to us. I hold no brief for such a drug. Its consideration should certainly be turned over to the health authorities. The treatment of the condition is undoubtedly the treatment of the patient. The underlying causes of allergy are the first to be investigated and the first to be treated.

The third statement in the summary, "Cinchophen exerts a direct stimulating action on the hepatic polygonal cells," is helpful, for if this drug does stimulate the hepatic polygonal cells, then its usefulness is assured because smaller doses may be used to great advantage and toxic results avoided. The authors are to be complimented on the title calling attention to a symptom which can be still further foretold by the routine use of known liver-function tests.

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NEWTON EVANS, M. D. (White Memorial Hospital, Los Angeles).—This clear and concise discussion of the most notable symptoms appearing in the victims of cinchophen poisoning is a valuable contribution. It should help in the accumulation of knowledge relative to this rare but often fatal sequel of the use of so valuable a therapeutic chemical compound.

The high mortality of these toxic attacks is suggested by the fact that in the present reported list one case in four was fatal. I understand the authors have previously reported four fatal cases and in addition have adequate records of seven more, making a total of fourteen originally collected cases, of which group eleven patients have died. The fact that of fourteen patients showing severe intoxications with jaundice only three have recovered indicates a very high percentage of mortality in those patients who have developed a severe jaundice.

The fact that the drug has been used extensively for many years and that the occurrence of severe poisoning is so unusual that it was not until 1925 that a fatal intoxication was reported, makes it appear that there must be some factors in the etiology of the attacks which are extremely variable. We naturally assume some unknown personal idiosyncrasy.

The fact of the relative infrequency of toxic sequelae, however, does not negative the reality of their existence. One can recall analogous relations in the use of other useful therapeutic agents. That of the newer arsenicals so commonly used in the treatment of syphilis and other similar infections are particularly apropos. The occurrence of aplastic anemia and related blood dyscrasias as well as cases of severe hepatic necroses in numerous instances, particularly after the use of neosalvarsan, can be regarded as indicating some type of peculiar susceptibility as contrasted to the great majority who have no such toxic manifestations.

Two practical lessons would appear obvious. First, the need of great caution and watchfulness in the administration of the drug by the physician, and second, the need of steps to minimize the widespread use of this powerful agent in the form of self-drugging through the agency of proprietaries and patent medicines.

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WILLIAM J. KERR, M.D. (University of California Medical School, San Francisco).—This paper on the subject of jaundice as an untoward effect following the administration of cinchophen is very timely. During the last four years a large number of cases have been reported in the literature where death resulted from the administration of cinchophen or compounds containing cinchophen. To date there have been upward of sixty such cases reported and, judging from discussions in various parts of the country, it may be assumed that there are many times this number of fatal cases as yet not reported in the literature. We have had three such cases in our Medical School during the last year, and there have been others where jaundice was probably on this basis.

The type of lesion which is usually seen in these patients represents a toxic cirrhosis with widespread necrosis of the hepatic cells. If the patient survives for a time there may be very active regeneration and then new tissue of the liver may be able to function, as far as carbohydrate metabolism is concerned; but new bile capillaries may not be connected with the bile ducts so that a secondary type of jaundice may result.

It is very difficult to detect those patients who would not be harmed by the administration of cinchophen. There has been some suggestion from our own experience that those patients who have had symptoms of chronic disease of the biliary tract or liver may be more susceptible to the drug. We have seen patients who developed marked evidence of cinchophen poisoning, resulting in death, from very small doses of cinchophen purchased at the corner drug store under various trade names. In one case it appeared that the patient had not taken more than thirty grains of cinchophen as a total dose. The widespread use of cinchophen and its compounds by the lay public as a result of extensive advertising in lay journals and newspapers offers a hazard to the public health which the medical profession and the state and government authorities should not tolerate. Certain restrictions are placed upon the sale of other dangerous drugs, and it would seem that it is high time that something should be done about the use of cinchophen. There is no doubt that cinchophen is a very valuable drug in controlling certain types of pain and is far superior to neocinchophen in this respect, but where the use of a drug is attended with so much risk it should be impossible for the layman to purchase this drug over the counter. Even in the hands of physicians who should be expected to know something about its use and its dangers there would, no doubt, be a certain number of fatalities. So far we have had no reports of serious damage to the liver from neocinchophen, but it should be more carefully studied with this possibility in mind. It seems to me that the California Medical Association, in conjunction with the State Board of Health and other state and national agencies, could do something about the control of the use of this drug.

## TYPHOID FEVER IN SAN FRANCISCO IN 1931 —APPARENTLY DUE TO SHELLFISH\*

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AND

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TYPHOID fever, although known to be a definitely preventable communicable disease, continues to occur, even in metropolitan areas, with a frequency altogether too high. Based on records of reported cases and deaths over a period of ten years, the disease in San Francisco has an expected yearly incidence of about thirty-five reported cases and eleven recorded deaths.

TABLE I INTERPRETATIONS

It is noteworthy that, in the series listed in Table 1, only in two instances, in 1928 and in 1931, are the numbers of reported cases in excess

TABLE 1.—*Listing the Reported Cases and Deaths Over the Decade 1922-1931 Inclusive*

Year	Typhoid Cases Reported	Deaths
1922 .....	25	12
1923 .....	36	17
1924 .....	28	14
1925 .....	39	12
1926 .....	38	14
1927 .....	40	10
1928 .....	76	20
1929 .....	34	6
1930 .....	38	8
1931 .....	68	9
Yearly average (excepting years 1928 and 1931).....	35	11

of forty for the year. The increased incidence in 1928 was due to an outbreak which was traced to pasteurized milk contaminated by a bacillus carrier operating a faulty capping machine.<sup>†</sup> Since the increased incidence in 1931 was unusual in certain respects, the data given in Table 2 are presented.

TABLE 2 INTERPRETATIONS

During the past ten years, cases of typhoid fever have been reported in San Francisco in every month of the year, and, indeed, in only four separate and nonconsecutive months were there no cases recorded. The expected incidence might be described as of the low-level, year-round type. Weekly reports through July and August showed slight increase over the normal expectancy. During the month of September, however, there was a definite and marked elevation in the epidemic index. This rather sharp rise was of short duration, but cases continued to be reported, while with less frequency, it is true, nevertheless on through October, November, December, and even January.

The week showing the maximum number of cases reported (twelve) was that ending September 19; it would be expected then that the dates of onset of a comparable maximum number

\* From the Department of Public Health, City and County of San Francisco.

† "Typhoid Fever Epidemic Occurring During the Summer of 1928," W. C. Hassler, M. D., J. A. P. H. A., February, 1930, 20:2, 137-146.